International Society for the Study of Fatty Acids and Lipids

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Food Labeling; Health Claims and Label Statements
Docket Nos. 91N-0103
Request for Scientific Data and Information
"Consumption of omega-3 fatty acids may reduce the risk of coronary heart disease"

Dear Sirs:

The International Society for the Study of Fatty acids and Lipids (ISSFAL) wishes to submit the enclosed information in response to your request for input regarding consumption of omega-3 fatty acids and coronary heart disease.

ISSFAL was founded in 1991 and currently has more than 350 members from over 40 countries worldwide. The members are scientists working in nutrition, physiology, pathology, biochemistry, cellular and molecular biology, and clinical medicine. The purpose of ISSFAL is to increase understanding of the role of dietary fatty acids and lipids in health and disease. In addition to promoting research on fatty acids and lipids, ISSFAL has an educational mission to assist in interpreting new scientific facts into sound nutritional advice for the public.

ISSFAL has been heavily involved in considering the nutritional effects and potential health benefits of omega-3 fatty acids. ISSFAL members have participated in many conferences dealing with this issue, including the Scientific Conference on Omega-3 Fatty Acids sponsored by the American Heart Association in 1994. In addition, ISSFAL was a sponsor of a recent international workshop on Omega-3 and Omega-6 Fatty Acids held in Bethesda, Maryland in May, 1999.

In response to your request for information, the Executive Committee of ISSFAL convened an Ad hoc Committee of experts to prepare a document summarizing and interpreting the existing scientific evidence regarding omega-3 fatty acids and coronary heart disease.

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The Committee is composed of eight members from four countries (Jorn Dyerberg, Norway; Claudio Galli, Italy; William Harris, USA; Reto Muggli, Switzerland; Arne Nordoy, Norway; Norman Salem, USA; Andrew Sinclair, Australia; and Arthur Spector, USA).
Much of the original nutritional, biochemical and clinical research on omega-3 fatty acids has been carried out by these individuals. The Committee has prepared the enclosed brief summation of the existing scientific data.

The ISSFAL Ad hoc Committee concludes that based on the available data, moderate increments in the intakes of omega-3, above the average'. consumption in most Western countries, are potentially beneficial for the prevention and treatment of coronary heart disease. Furthermore, the Committee concludes that there is no risk associated with the consumption of these moderate amounts of omega-3 fatty acids. Therefore, ISSFAL urges the FDA to reevaluate its labeling position regarding health claims for omega-3 and coronary heart disease.

Sincerely yours,

Claudio Galli (Italy)*
President of ISSFAL

On behalf of the Ad hoc Committee :

A. Spector (USA) Vice President ISSFAL
J. Dyerberg (DK) Past President ISSFAL
W. Harris (USA)
R. Muggli (CH)
A. Nordoy (N)
N. Salem (USA)
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The purpose of the society is to increase understanding through research and education of the role of dietary fatty acids

Omega 3 Polyunsaturated Fatty Acids and Coronary Heart Disease Prevention

An ISSFAL document

Introduction

Evidence that ω3 polyunsaturated fatty acids may protect against coronary heart disease has accumulated over the past 25 years. In the 1970s, Danish investigators studied heart disease rates in native peoples of Greenland and discovered significantly lower levels of acute myocardial infarction in Eskimos compared with age- and sex-matched Danes. On further investigation, Bang and Dyerberg concluded that the high level of ω3 fatty acids in their native diet may have accounted for the low rates of coronary heart disease (CHD). In studies of other populations such as the Japanese, higher fish intake has also been associated with lower rates of heart disease. In addition to replacing meat (with its saturated fatty acids and cholesterol), fish serves as the best source of long-chain ω3 fatty acids. By the mid 1980's, ω3 fatty acids became the focus of intense investigation.

Animal and clinical investigations into the functional effects, health impact, and metabolism of ω3 fatty acids have identified several promising uses of fish oil in disease prevention and treatment. Although their greatest impact may be in the arena of cardiovascular disease, a beneficial role for this class of fatty acids has clearly been implicated in several other systems. For example, it now appears that ω3 fatty acids are essential nutrients required in utero for proper development of nervous tissues. The ω3 fatty acid most clearly needed is docosahexaenoic acid (DHA; C22:6ω3), the longest and most unsaturated of all known dietary fatty acids, which is present in high concentrations in specialized membranes in the retina and the synapses. It appears that consumption of the plant-derived precursor of DHA, a-linolenic acid (LNA; C18:3ω3), may provide enough DHA for adults, through the conversion of the ω3 precursor to the final product. However, infants may need direct delivery of DHA (and arachidonic acid; C20:4ω6) from the placenta for proper brain development. There is currently tremendous interest in fortifying infant formulas (especially preterm) with DHA, although important unanswered questions remain and are currently being addressed in clinical trials. Another area of intense ω3 research is immunology. From rheumatoid arthritis, to psoriasis, IgA nephropathy and colitis many research groups are exploring the healing or preventive potential utility of this class of natural products. Another possible area in which the anti-inflammatory effects of ω3 fatty acids may have a major beneficial effect is in atherosclerosis.

Heart Disease

Omega 3 fatty acids first attracted the attention of the medical community in the arena of heart disease prevention. Although ω3 fatty acids may play important roles in immune and inflammatory responses, their impact on platelet function and lipoprotein metabolism

attracted most of the early attention. The recognition that eicosapentaenoic acid (EPA), the other major marine-derived ω3 fatty acid, in addition to replacing arachidonic acid in cells and tissues, was a substrate for cyclooxygenase, and that thromboxane A_3 was far less biologically active than its arachidonic acid-derived counterpart thromboxane A_2, helped explain the prolonged bleeding times in Greenland Eskimos. In addition, PGI_3, the antiaggregatory prostaglandin derived from EPA has effects comparable to those of the AA-derived PGI_2. Subsequent research revealed that the other 3-series eicosanoids derived from EPA (e.g., PGE_3, leukotriene B_5) also had reduced physiological activity relative to their 2-series counterparts. It was these differences in metabolism between the EPA and AA derived metabolites that are likely to be the basis for not only the less thrombogenic vigor observed in subjects taking fish oils, but also for their anti-inflammatory properties. EPA-derived leukotrienes (LT-5 series) in fact have less potent leukocyte activating effects than their AA-derived (LT-4 series) counterparts. Thus, part of the anti-atherogenic mechanism of ω3 fatty acids is likely due to their impact on eicosanoid metabolism.

Lipoprotein metabolism was also affected by ω3 fatty acids, but apparently not via alterations in the eicosanoid system. The ability of these fatty acids to reduce serum triglyceride levels (both fasting and postprandial) has been well-established. The mechanism of the triglyceride-lowering effect involves an inhibition of hepatic triglyceride synthesis and secretion but a possible effect on triglyceride clearance is still being investigated. Total cholesterol levels usually do not change, whereas small increases in HDL-cholesterol have frequently been reported. Like the triglyceride-lowering fibrate drugs, ω3 fatty acid treatment can increase LDL-cholesterol levels, particularly in subjects with significant hyper-triglyceridemia; in other patients changes are uncommon. Non-lipid effects on CHD risk factors such as fibrinogen, blood viscosity, platelet aggregation or endothelial function may also explain some of the beneficial effects of fish oils on thrombosis and atherosclerosis. Finally, ω3 fatty acids may also play a role in the reduction of blood pressure and thereby may reduce the risk for CHD.

Animal Studies

In one of the first well-controlled animal trials in this area, Weiner et al. reported that pigs fed an atherogenic diet supplemented with 30 ml/d of cod liver oil for 8 months developed significantly less atherosclerosis than did the control animals. Of particular interest was the lack of association between LDL levels and atherosclerotic changes in the arteries of pigs given fish oil; in fact, the LDL-cholesterol concentrations were higher in the fish oil group. Davis et al. studied the effects of feeding coconut oil with two different doses of fish oil to Rhesus monkeys. In this study, feeding higher levels of fish oil depressed HDL levels. Nevertheless, there was a clear dose-response effect between fish oil intake and less arterial plaque. These observations suggest that ω3 fatty acids can improve the atherogenic milieu even in the face of adverse changes in serum lipids. It is important to note, however, that

no adverse effects on serum lipoproteins have been observed in humans consuming "practical" levels (<3 g/d) of ω3 fatty acids.

Fish oil may play a role in preventing reperfusion injury to the heart and brain. In one study, rats were fed 12% of calories either as corn oil or as fish oil for a month; myocardial ischemia was induced by tying off the left main coronary artery for 15 minutes and then reperfusing for 6 hours. Among the rats fed fish oil, 76% survived the "heart attack" and 14% had ventricular tachycardia and fibrillation; among those fed corn oil, the percentages were 41% and 90%, respectively. Dog studies have shown that acute infusion of EPA and DHA can reverse ventricular fibrillation, strengthening the rationale for the use of these fatty acids in preventing rhythm disorders. There are several potential mechanisms to explain the protective, mainly anti-arrhythmic, effects of ω3 fatty acids on heart function. Cell studies, carried out by Leaf and colleagues have shown that the presence of w-3 FAs in the myocardial cell membranes electrically stabilizes the cells and prolongs the relative refractory period. Because population-based casecontrol and epidemiological studies have associated ω3 FAs with decreased cardiac death (Dolecek 1992; Siscovick et al 1995), these electrop hy siologic changes may be most important clinically.

Human Studies

There have been several epidemiological studies comparing CHD rates between fish eating and non-fish eating populations, and across the spectrum of fish consumption within populations. Although these studies have largely supported a cardioprotective effect of fish, the link to ω3 fatty acids has been more difficult to establish due to the low intake estimates characteristic of diet survey studies. These uncertainties have been addressed, however, in several prospective, randomized, intervention trials using either oily fish, or more recently, encapsulated fish oils or purified ω3 fatty acids.

Intervention Studies. The first study to prospectively explore the cardioprotective effect of ω3 fatty acids in a secondary prevention population was the Diet and Reinfarction Trial. Burr et al. studied 2,013 men who had survived a heart attack. Half were advised to eat oily fish twice a week or to take fish oil capsules, in an amount equivalent to the ω3 fatty acid content of the fish diet, while the other half were advised only to eat a prudent diet. Survival over the subsequent 2 years was followed. The researchers used food diaries and blood EPA levels to confirm compliance. The group advised to consume oily fish showed a 29% reduction in overall, 2-year mortality compared with the control group. Interestingly, there were no significant differences between groups in total ischemic heart disease *events* because more subjects in the fish oil group experienced *nonfatal* myocardial infarctions while more subjects in the control group experienced *fatal* myocardial infarctions. These results pointed to a possible protective effect for ω3 fatty acids during ischemia and reperfusion, as already indicated by animal studies.

Another prospective, randomized clinical trial using ω3 fatty acids was reported by Singh et al. Patients presenting with suspected myocardial infarctions (n=360) were randomized to placebo, fish oil (2 g of EPA+DHA per day) or mustard seed oil (containing 2.9 g of α-linolenic acid per day). After one year, CHD events were significantly reduced in both ω3 fatty acid groups. Von Schacky and colleagues recently reported a small but statistically significant reduction in angiographically-determined CHD progression in a study which provided 6 g of ω3 fatty acids for 3 months followed by 3 g/d for 21 months or placebo in 223 patients. There were 7 cardiovascular events in the control group and 2 in the ω3 group (p=0.10). In a study of the effects of ω3 fatty acids on coronary artery bypass graft patency, efficacy was highly correlated to serum ω3 fatty acid levels, with those patients achieving the highest serum levels having an odds ratio for graft occlusion of 0.49 compared to those with the lowest increment in serum phospholipid ω3 fatty acid levels. This finding illustrates the perhaps obvious fact that differences in compliance and individual metabolism of ω3 fatty acids may contribute to differences in clinical outcomes, and suggests that ω3 fatty acid levels in the blood be assessed in all outcome studies.

The overall protective effects of ω3 fatty acids on heart function, in addition to the previously mentioned anti-arrhythmic activities may be related to improved heart rate variability. Decreased heart rate variability has been in fact strongly associated with increased risk of sudden death, and in a randomized trial, evaluating the effects of fish oil vs. placebo in post-infarction patients, significant increases in R-to-R variability were observed in the ω-3 FA-treated patients. Patients with higher fish intakes have also been shown to have greater heart rate variability.

Increasingly, the serum triglyceride level is being recognized as an important independent risk factor for CHD. The most well-characterized effect of EPA and DHA is their ability to reduce serum triglyceride levels. EPA+DHA, at doses of 3-5 g/d, will significantly reduce triglycerides by 20-30%, and 3.4 g/d has been shown to reduce levels by nearly 50% in patients with severe (>750 mg/dL) hypertriglyceridemia. Smaller intakes (about 1 g/d) usually do not lower fasting triglycerides (e.g., in GISSI Prevention Trial, triglycerides were reduced by only 3%). However, even low-dose fish oil may reduce postprandial triglyceride levels, and this could contribute to the benefit.

The most recent test of the effects of ω3 fatty acids on CHD morbidity and mortality was the GISSI-Prevention Trial. This study was conducted in Italy and included 11,324 patients with known CHD. In a factorial design, 2830 of the patients were assigned to take vitamin E (300 mg/d); another 2836 were given 850 mg of ω3 fatty acids daily; another 2830 given both and the final 2828 received neither. After 3.5 years of follow up, an intention-to-treat analysis revealed that total mortality in the patients given ω3 fatty acids was 20% lower

than in those patients not so treated, and the incidence of sudden cardiac death was reduced by 45%. Vitamin E showed a beneficial trend but it was not statistically significant. These results were achieved despite the fact that over 25% of patients reported that they stopped taking the capsules. The finding of the GISSI-Prevention study provides strong support for the use of ω3 fatty acids in secondary prevention of acute coronary syndromes. The mechanism by which ω3 fatty acids protect against cardiac death are not known with certainty, but it may relate to their ability to prevent cellular damage during periods of ischemic stress.

In conclusion, the evidence for a protective role of ω3 fatty acids in CHD is becoming clearer and firmer, especially for secondary prevention. Intakes of approximately 800- 1,000 mg per day appear to be a prudent approach for the latter group of patients. The safety of intakes of up to 3,000 mg per day has been endorsed by the recent ruling of the FDA that this level of EPA+DHA (from menhaden oil) is generally recognized as safe (GRAS) for inclusion in the American food supply. Additionally, high linoleic acid intakes should be discouraged since they antagonize the effective incorporation of the ω3 fatty acids into biomembranes.

The International Society for the Study of Fatty Acids and Lipids (ISSFAL) strongly emphasizes, on the basis of the scientific evidence briefly reviewed above, the likely beneficial effects of low to moderate intakes of ω3 fatty acids regarding coronary heart disease, hypertriglyceridemia, thrombosis and inflammation. The estimated intakes of EPA + DHA in most countries, especially in those on typical Western style diets, are in the range of 100 mg/day or less (eg. Eaton et al 1998, Sinclair & Vingrys 1998). Recommendations for the general population, have been made in UK (UK Department of Health, 1997) and Europe (de Deckere et al 1998) of levels of approximately 200mg/day. Recommendations to raise these values from a minimum of 200 up to 650 mg / day for the general population were recently made by a group of experts at a meeting held at the NIH, (Workshop on the Essentiality of and Dietary Reference Intakes for Omega-6 and Omega-3 Fatty Acids, April 7-9, 1999). The lack of adverse effects at the above intakes provides additional support for recommending greater consumptions of these fatty acids by the general population. ISSFAL would therefore firmly recommend that the FDA reevaluates its position concerning the claim “consumption of omega 3 fatty acids may reduce the risk of coronary heart disease” in relation to health claims for use in the labeling of dietary supplements.

Suggested Reading

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